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Note

Stability of benzylpenicillin potassium and ampicillin in an elastomeric infusion pump☆

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ABSTRACT

Some infectious diseases, such as infective endocarditis, osteomyelitis, and abscesses, require treatment with long-term intravenous antimicrobial treatment. Therefore, the patient is required to stay in the hospital to receive therapy, which lowers their quality of life. Establishing an outpatient parenteral antimicrobial therapy (OPAT) by continuous infusion pump is desired in Japan to overcome these issues. However, the 24-h stability of antimicrobial agents dissolved in infusion solutions is unclear. Thus, we investigated the stability of antimicrobial agents in five different infusion solutions in a clinical setting. Benzylpenicillin potassium (PCG) and ampicillin (ABPC) were dissolved separately in five different infusion solutions and kept at 25 or 31.1 °C for 24 h. The residual ratios were determined by high-performance liquid chromatography (HPLC). Dissolved PCG in acetate ringer solution remained stable for 24 h at temperatures of 25 and 31.1 °C (101.7 ± 1.4% and 92.9 ± 1.3%, respectively). In addition, the PCG solution did not adsorb onto the elastomeric infusion pump after 24 h at 31.1 °C. PCG dissolved in acetate ringer solution was also stable for 10 days after being kept in an elastomeric infusion pump at 4 °C (99.7 ± 0.5%). ABPC was unstable in all of the tested infusion solutions and temperatures. Based on our results, PCG in acetate ringer solution can be used in OPAT with continuous infusion pumps.

Outpatient parenteral antimicrobial therapy (OPAT) is the administration of intravenous antimicrobial therapy that can be performed in the homes of outpatients. It is well established and frequently used in several countries since its first report in 1974 [1]. The guidelines for OPAT were published by the Infectious Diseases Society of America (IDSA) in 2004 and is used around the world [2,3]. OPAT is considered useful since it reduces medical expenditure due to hospital stays and improves the quality of life [4,5]. However, it is not widely practiced in Japan due to several issues such as insufficient health insurance coverage for the device, insufficient information regarding drug stability [6], and lack of a medical support care system. Some possible models for OPAT include its implementation in 1) a hospital outpatient/clinic setting, 2) the patient's home and administered by a health care professional, and 3) the patient's home and self-administered or administered by a caregiver after training by OPAT staff [7]. For each OPAT model, intravenous access devices and continuous infusion pump systems (syringe pumps, mechanical pumps, or elastomeric infusion pumps) are required. Elastomeric infusion pumps are frequently used in Australia and Singapore for OPAT [4,8] and are relatively more convenient and economic than other pump systems. In addition, administration by elastomeric infusion pumps is easier to perform. Hase et al. reported that a combination of elastomeric infusion pumps and care attendant service may facilitate the use of OPAT in Japan [5]. However, they also emphasized the need for clarifying information regarding drug stability.

OPAT is used to treat soft tissue infections, osteomyelitis, infective endocarditis (IE), or abscesses [2,3,9], that require long-term antimicrobial chemotherapy. However, the antimicrobial agents allowed for use in OPAT are limited due to their stability in aqueous solutions. Most β-lactam antibiotics, except for benzylpenicillin potassium (PCG) and ampicillin (ABPC), are stable and are eligible to be used in OPAT [9]. However, the broad spectrums of cephalosporins or carbapenems are not suitable to treat infectious

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diseases, such as IE, that are often caused by *Streptococcus viridans* and *Streptococcus bovis* [10]. Therefore, establishing OPAT with infusion pumps using PCG or ABPC may promote better antimicrobial stewardship. However, they are not used in OPAT because their stabilities in solution are unknown. Moreover, the excipient content in the antimicrobial agent varies based on the country of manufacture. Compared to those manufactured in foreign counties, PCG produced in Japan does not contain buffering agents and is thought to be unstable in aqueous solutions. Therefore, the stability data of antimicrobial agents produced in foreign countries may not be applicable in Japan. Based on a previous study, the stabilities of PCG and ABPC were tested at 4 and 25 °C [9]; however, in clinical practice, the solution temperature is higher than those investigated in these studies [9]. Increasing temperature may accelerate the degradation of antimicrobial agents. Therefore, drug stability information pertaining to the Japanese clinical setting is required.

The purpose of this study was to clarify the stability of β-lactam antibiotics that are manufactured in Japan, i.e., PCG and ABPC, under storage (4 °C) and at the time of administration (25 °C, 31.1 °C).

Both PCG and ABPC standards as well as phosphoric acid were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). PCG (penicillin G potassium) and ABPC for use in injections were purchased from Meiji Seika Pharma Co., Ltd. (Tokyo, Japan). Acetonitrile was purchased from Kanto Chemical Co., Inc. (Tokyo, Japan). Sodium dihydrogen phosphate dihydrate and potassium dihydrogen phosphate were purchased from Nacalai Tesque (Kyoto, Japan). Acetate ringer solution was purchased from Kowa Pharm Co., Ltd. (Tokyo, Japan). Saline solution and 5% dextrose solution were purchased from Otsuka Pharma Co., Ltd. (Tokyo, Japan). Dextrose-electrolyte solution without potassium chloride was purchased from Terumo Co., Ltd. (Tokyo, Japan). Dextrose-electrolyte solution with potassium chloride was purchased from Terumo Co., Ltd. (Tokyo, Japan). Baxter infuser LV10 was purchased from Baxter International Inc. (Illinois, USA).

A Baxter infuser LV10 pump is an elastomeric infusion pump that discharges solution at 10 mL/h and is designed for volumes up to 240 mL. According to the scientific statement for the therapy of infective endocarditis, the PCG and ABPC doses for IE therapy are 24 million units and 12 g per day, respectively [11]. Therefore, the maximum concentration of PCG and ABPC was determined to be 100 thousand units/mL and 0.05 g/mL, respectively. The stability of these antimicrobial agents was investigated at 25 and 31.1 °C since the elastomeric infusion pump is designed to function at 31.1 °C. The antimicrobial agents were dissolved in five different infusion solutions and were kept at 25 or 31.1 °C in polypropylene centrifuge tubes. The residual ratios of PCG and ABPC at 0, 1, 2, 4, 6, 8, and 24 h were determined by HPLC.

To determine the 24-h stability of PCG in the elastomeric infusion pump, PCG was dissolved in acetate ringer solution and kept at 31.1 °C for 24 h in the elastomeric infusion pump. The residual ratio of PCG was determined by HPLC. In addition, PCG was dissolved in acetate ringer solution and kept at 4 °C in the elastomeric infusion pump. The residual ratio of PCG at 0, 1, 3, 5, 7, and 10 days were determined by HPLC.

The concentrations of PCG and ABPC were measured by HPLC, as described previously [12,13]. The PCG and ABPC standards were dissolved in diluted water. PCG and ABPC were dissolved separately in five different infusion solutions and kept at arbitrary temperatures and time before measurement by HPLC. The HPLC systems consisted of a HITACHI L-7100 pump, HITACHI L-7300 column oven, and HITACHI L-4200 UV detector. A TSK-GEL ODS-80TM column (4.6 mm × 250 mm, 5 μm, Tosoh Co., Ltd., Tokyo, Japan) was used as the stationary phase. The mobile phase consisted of 100 mM phosphate buffer (pH3.0) − acetonitrile (65:35, v/v) for PCG and 10 mM potassium phosphate (pH4.7) − acetonitrile (85:15, v/v) for ABPC. The flow rate was 1.0 mL/min. The detection UV wavelength for PCG and ABPC were 210 and 219 nm, respectively.

Dissolved PCG in acetate ringer solution remained stable at 25 and 31.1 °C after 24 h (101.7 ± 1.4% and 92.9 ± 1.3%, respectively) (Fig. 1A and C). After 24 h and at 25 °C, the residual ratios of PCG in saline solution, 5% dextrose solution, dextrose-electrolyte solution without potassium chloride, and dextrose-electrolyte solution with potassium chloride were 52.1 ± 0.8, 56.6 ± 1.0, 83.0 ± 1.2, and 84.6 ± 1.1%, respectively (Fig. 1A). Furthermore, at 31.1 °C, the stability of PCG dissolved in saline solution, 5% dextrose solution, dextrose-electrolyte solution without potassium chloride, and dextrose-electrolyte solution with potassium chloride were 11.4 ± 0.3, 13.6 ± 0.0, 46.8 ± 1.1, and 48.6 ± 0.9, respectively (Fig. 1C). At 25 and 31.1 °C, the pH of these solutions immediately decreased when PCG was added; however, this decrease was less pronounced in the acetate ringer solution (Fig. 1B and D).

The stability and pH of PCG in the elastomeric infusion pump were 91.6 ± 0.8% and 5.3 ± 0.03, respectively, after 24 h at 31.1 °C. The residual ratio of PCG dissolved in acetate ringer solution after 10 days at 4 °C was 99.7 ± 0.5% (Fig. 2A). The pH of the PCG acetate ringer solution slightly decreased after 10 days at 4 °C (6.8 ± 0.05 at day 0−5.9 ± 0.02 at day 10) (Fig. 2B).

The residual ratios of ABPC fell below 90% at temperatures of 25 and 31.1 °C (Fig. 3A and C). The residual ratios of ABPC dissolved in acetate ringer and saline solution after 24 h at 25 °C were higher than the other solutions (acetate ringer solution, 78.5 ± 0.9%; saline solution, 77.8 ± 1.5%; 5% dextrose solution, 44.4 ± 0.6%; dextrose-electrolyte solution without potassium chloride, 53.9 ± 1.0%; dextrose-electrolyte solution with potassium chloride, 53.2 ± 1.0%). The residual ratios of ABPC after 24 h at 31.1 °C was lower than at 25 °C (acetate ringer solution, 72.6 ± 0.9%; saline solution, 73.2 ± 1.6%; 5% dextrose solution, 36.2 ± 0.5%; dextrose-electrolyte

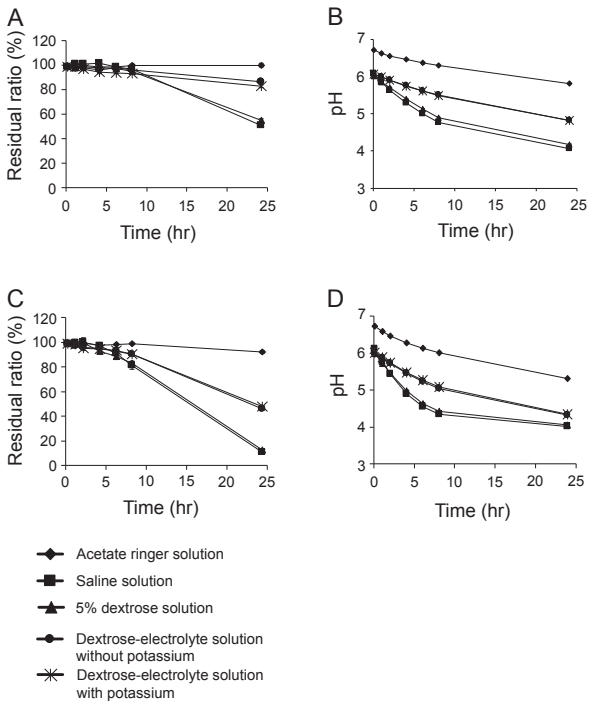

Fig. 1. The stability and pH alteration of PCG at 25 and 31.1 °C. PCG was dissolved in each infusion solution and was kept at 25 or 31.1 °C for 24 h. (A) The residual ratios and (B) pH alteration by PCG at 25 °C were determined by HPLC. (C) The residual ratios and (D) pH alteration by PCG at 31.1 °C were determined by HPLC. Data are expressed as the mean ± S.D (n = 3).

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